

**REMARKS**

Claim 11 has been amended to add the term “decellularized.” Support for this amendment can be found, for example, on page 17, lines 5 to 7, of the specification as filed.

**CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a):**

**(1) Claims 11-15 and 17-19 over Badylak (2002) in view of Badylak (2007)**

The Examiner has rejected claims 11-15 and 17-19 under 35 U.S.C. § 103(a) as being obvious over WO 98/25637 or U.S. Patent No. 6,379,710 (“Badylak (2002)”) each in view of U.S. Patent No. 7,175,841 (“Badylak (2007)”). The arguments that refer to “Badylak (2002)” in this response apply to either WO 98/25637 or Badylak (2002) because Badylak (2002) is a U.S. patent corresponding to WO 98/25637. The Examiner indicates that Badylak (2002) teaches a tissue graft composition comprising liver basement membrane prepared by removing the cellular components from liver tissue. However, the Examiner indicates that Badylak (2002) does not teach a specified DNA content of the liver basement membrane.

The Examiner contends that Badylak (2007) teaches an improved tissue graft construct comprising submucosa of a warm-blooded vertebrate and a preselected group of eukaryotic cells to enhance the repair of damaged or diseased tissue *in vivo*. In addition, the Examiner asserts that Badylak (2007) describes the DNA content of cartilaginous tissue, formed on an intestinal submucosa composition, to be about 0.86 +/- 0.2  $\mu$ g DNA/mg dry weight. The Examiner argues that cartilaginous tissue contains chondrocytes that produce extracellular matrix material and that cartilaginous tissue is therefore more representative of the claimed liver basement membrane than intestinal submucosa. The Examiner further argues that the DNA content of 0.86 +/- 0.2  $\mu$ g DNA/mg dry weight is close to the claimed DNA content of 0.303 +/-

0.263  $\mu$ g DNA/mg dry weight. Therefore, according to the Examiner, it would have been *prima facie* obvious for a person skilled in the art to employ the tissue graft composition comprising liver basement membrane of Badylak (2002) with the DNA content in the tissue graft taught by Badylak (2007) to arrive at the invention described by Applicants' claims.

Applicants respectfully traverse the Examiner's rejection. Independent claims 11 and 19 of the instant application specify "decellularized" basement membrane, wherein the DNA content is within a set of values with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. Thus, claims 11-15 and 17-19 are not obvious under 35 U.S.C. § 103(a) over Badylak (2002) in view of Badylak (2007).

**A. CARTILAGINOUS TISSUE IS NOT SIMILAR TO APPLICANTS' CLAIMED GRAFT CONSTRUCT COMPRISING DECELLULARIZED BASEMENT MEMBRANE**

The DNA content of cartilaginous tissue formed on an intestinal submucosa composition as described in Badylak (2007) is irrelevant to the invention as defined by Applicants' claims. Badylak (2007) describes the DNA content of cartilaginous tissue, formed on an intestinal submucosa composition, to be about 0.86 +/- 0.2  $\mu$ g DNA/mg dry weight (see column 21, lines 11-29). Importantly, this DNA content is an estimated quantification of the DNA content of chondrocytes, grown *in vitro* on intestinal submucosa. The estimate is obtained by subtracting the DNA content for intestinal submucosa from the DNA content for intestinal submucosa in combination with chondrocytes (see column 20, lines 60-65, column 21, lines 9-29, and column 22, lines 20-25 of Badylak (2007)).

In contrast, Applicants' amended independent claims 11 and 19 are directed to purified basement membrane graft compositions comprising "decellularized" basement membrane wherein the DNA content is within a set of values with an average of 0.303 and a

standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. Therefore, the Examiner's contention that the cartilaginous tissue described in Badylak (2007) is closer to basement membrane than intestinal submucosal tissue is incorrect. The cartilaginous tissue described in Badylak (2007) is a **cellular** composition containing chondrocytes. The DNA content of a **cellular** composition cannot render obvious the DNA content of a **decellularized** composition as claimed in Applicants' amended claims 11 and 19.

Thus, the range of DNA content cited by the Examiner for the **cellular** composition described in Badylak (2007) (i.e., 0.86 +/- 0.2  $\mu$ g DNA/mg dry weight) cannot render obvious the DNA content of basement membrane as required by Applicants' claims because Applicants' claims are directed to **decellularized** basement membrane. Accordingly, the DNA content of the cellular composition described in Badylak (2007) cannot be relied upon to support a rejection of obviousness under 35 U.S.C. § 103.

**B. OBVIOUSNESS OF RANGES**

Moreover, Applicants point the Examiner to MPEP § 2144.05, regarding the obviousness of ranges in claims. According to the MPEP, if "the claimed ranges overlap or lie inside ranges disclosed by the prior art[,] a *prima facie* case of obviousness exists." MPEP § 2144.05(I) (quoting *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976)). Furthermore, "a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties." *Id.* (quoting *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985)).

A careful analysis of Applicants' independent claims 11 and 19 reveals that the ranges in Applicants' claims do *not* overlap or lie inside ranges disclosed by the prior art (i.e., Badylak (2007)). Applicants' claims describe a range of DNA content of "decellularized"

basement membrane wherein the DNA content is within a set of values with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. Taking into account the stated standard deviation, the claims thus describe a DNA content of basement membrane with a range of 0.040  $\mu$ g DNA/mg dry weight to 0.566  $\mu$ g DNA/mg dry weight.

In contrast, the range of the DNA content of intestinal submucosa tissue as disclosed by Badylak (2007) does *not* overlap with Applicants' claimed range. Badylak (2007) describes that the DNA content of intestinal submucosa tissue is 2.04 +/- 0.1  $\mu$ g DNA/mg dry weight. Taking into account the stated standard error, Badylak (2007) thus describes the DNA content of intestinal submucosa tissue with a range of 1.94  $\mu$ g DNA/mg dry weight to 2.14  $\mu$ g DNA/mg dry weight.

For the Examiner's convenience, the ranges as described in Applicants' claims and in the prior art (i.e., Badylak (2007)) are summarized in Table 1:

**Table 1.**

<b>Claims of Instant Application or Prior Art Reference</b>	<b>Tissue Type</b>	<b>DNA Content (<math>\mu</math>g DNA/mg dry weight)</b>	<b>Range of DNA Content (<math>\mu</math>g DNA/mg dry weight)</b>
Independent claims 11 and 19 (instant application)	Basement membrane	0.303 +/- 0.263	0.040 - 0.566
Badylak (2007) (prior art reference)	Intestinal submucosa tissue	2.04 +/- 0.1	1.94 - 2.14

Clearly, Applicants' claimed range in independent claims 11 and 19 of the instant application does *not* overlap with the range described in the prior art (see Table 1, above).

Moreover, the range in Applicants' claims and the DNA content range described in Badylak (2007) are not close enough that one skilled in the art would have expected them to have the same properties. It is known in the art that a lower DNA content in graft compositions correlates with a reduction in immunogenicity (see, for example, an abstract by Narita et al.,

submitted herewith as “Exhibit A”). Accordingly, one skilled in the art would not have expected a basement membrane with a DNA content range as required by Applicants’ claims (i.e., 0.303 +/- 0.263  $\mu$ g DNA/mg dry weight) to have the same properties as the range described in Badylak (2007) (i.e., 2.04 +/- 0.1  $\mu$ g DNA/mg dry weight). Therefore, the Examiner has not established a *prima facie* case of obviousness regarding obviousness of claimed ranges as required by MPEP § 2144.

**C. ALL CLAIM LIMITATIONS MUST BE TAUGHT OR SUGGESTED BY THE PRIOR ART**

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Therefore, in order for Applicants’ invention to be rendered obvious under 35 U.S.C. § 103, the combination of references relied upon by the Examiner must teach each and every element of Applicants’ claims.

Badylak (2002) and Badylak (2007) describe a DNA content range higher than what is claimed in Applicants’ independent claims 11 and 19. It is not obvious from the teachings of the prior art that a skilled artisan could achieve the DNA purity level for basement membrane grafts as claimed by Applicants. Furthermore, as explained above, the range specified by Applicants in independent claims 11 and 19 does *not* overlap with the ranges described in the prior art. Accordingly, the claim limitations in claims 11 and 19 (i.e., decellularized basement membrane wherein the DNA content is 0.303 +/- 0.263  $\mu$ g DNA/mg dry weight) are not taught by the prior art cited by the Examiner. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness because all of the limitations of Applicants’ claims are not taught by the prior art, and the rejection of claims 11-15 and 17-19 under 35 U.S.C. § 103 is improper. Withdrawal of the rejection of claims 11-15 and 17-19 under 35 U.S.C. § 103(a) over Badylak (2002) in view of Badylak (2007) is respectfully requested.

**(2) Claim 19 over either Robinson et al. or Brendel et al. in view of Badylak (2007)**

**A. CARTILAGINOUS TISSUE IS NOT SIMILAR TO APPLICANTS' CLAIMED GRAFT CONSTRUCT COMPRISING DECELLULARIZED BASEMENT MEMBRANE**

As discussed above, the DNA content of a ***cellular*** composition as described in Badylak (2007) cannot render obvious Applicants' claims directed to a ***decellularized*** basement membrane. The two compositions are inapposite to each other. Accordingly, the Examiner's reliance on the DNA content of the cellular composition described in Badylak (2007) cannot support a rejection of obviousness under 35 U.S.C. § 103.

**B. OBVIOUSNESS OF RANGES**

As discussed above, the range of the DNA content of basement membrane as described in independent claims 11 and 19 of the instant application does *not* overlap with the range for the DNA content of the intestinal submucosa composition described in Badylak (2007). Furthermore, the DNA content range required by in Applicants' claims and the DNA content range described in Badylak (2007) are not close enough that one skilled in the art would have expected them to have the same properties. Therefore, the Examiner has not established a *prima facie* case of obviousness based on Robinson et al. or Brendel et al. in view of Badylak (2007).

**C. ALL CLAIM LIMITATIONS MUST BE TAUGHT OR SUGGESTED BY THE PRIOR ART**

As explained previously, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490

F.2d 981, 180 USPQ 580 (CCPA 1974). Therefore, in order for Applicants' claims to be rendered obvious under 35 U.S.C. § 103, the combination of references relied upon by the Examiner must teach each and every element of Applicants' invention, as defined by claim 19.

The prior art combination of either Robinson et al. (*European Journal of Biochemistry/FEBS*, 1980, 11(2): 485-490) or Brendel et al. (*Advances in Experimental Medicine and Biology*, 1980, 131: 89-103) in view of Badylak (2007) fails to support a rejection under 35 U.S.C. § 103 because all of the claim limitations in Applicants' claim 19 are not taught by the cited reference combination. Specifically, the prior art does not teach the DNA content range required by Applicants' claim 19 (see detailed arguments above for the rejection under 35 U.S.C. § 103 over Badylak (2002) in view of Badylak (2007)).

Claim 19 requires that the DNA content of Applicants' claimed "decellularized" basement membrane is within a set of values with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. None of the cited prior art references teach a DNA content range of a decellularized tissue with an average of 0.303 and a standard deviation of 0.263 micrograms of DNA per milligram of dry weight of the basement membrane. This DNA content range was not identified in the prior art, and it was not obvious that the DNA purity level claimed by Applicants could be achieved for basement membrane grafts.

Therefore, based on all of the foregoing arguments, claim 19 of the instant application is not obvious over the cited reference combination. Withdrawal of the rejection of claim 19 under 35 U.S.C. § 103(a) over either Robinson et al. or Brendel et al. in view of Badylak (2007) is respectfully requested.

claim 19 under 35 U.S.C. § 103(a) over either Robinson et al. or Brendel et al. in view of Badylak (2007) is respectfully requested.

**CONCLUSION**

The foregoing amendments and remarks are believed to fully respond to the Examiner's rejections. The claims are in condition for allowance. Applicants respectfully request allowance of the claims, and passage of the application to issuance.

Respectfully submitted,



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